

IN THE SPECIFICATION:

Please amend the specification as follows:

Please replace the last paragraph on page 1 bridging page 2 with the following rewritten paragraph:

Methods for diagnosing human cancer using a biological sample, such as serum, are known. For example, methods for diagnosing cancer by measuring a tumor marker in a biological sample such as serum have been developed. With regard to the tumor marker, for example, prostatic specific antigen (PSA) which is a marker of prostatic cancer, squamous cell carcinoma related antigen (SCC) which is a marker of cervical carcinoma, alpha-fetoprotein (AFP) which is a marker of liver cancer, and carcinoembryonic antigen (CEA) which is a marker of colon cancer are known. With regard to ~~[[high]]~~ highly sensitive methods for measuring ~~[[the]]~~ tumor ~~marker~~ markers, for example, a radioimmunoassay (RIA), an enzyme immunoassay (EIA), and a fluorescence immunoassay (FIA), in which different monoclonal antibodies against the tumor marker are used, have been developed.

Please replace the first full paragraph on page 2 with the following rewritten paragraph:

Conventional tumor markers are targeted to diagnose cancer of a particular organ, and every tumor marker can only be used to diagnose cancer of ~~[[only]]~~ a particular organ. Additionally, some organs do not have a proper cancer marker. Therefore, the conventional tumor markers cannot be widely applied to the diagnosis of cancer in general. Furthermore, the conventional tumor markers are not cancer-

Application Serial No.: 10/559,311

specific substances in a precise sense. Namely, the tumor markers are also produced in a normal living body at some level. Therefore, these markers are difficult to be used in the determination of early stage ~~[[of]]~~ cancer when the production level of the tumor marker is low. Additionally, it is ~~and are difficult to be used~~ use these markers in the determination of cancer susceptibility, which means a tendency to suffer from cancer.

Please replace the last paragraph on page 2 bridging page 3 with the following rewritten paragraph:

Therefore, it is an object of the present invention to provide a method for investigating the presence of cancer cells whatever the organ or the cause of the carcinogenesis ~~[[is]]~~. Specifically, it is an object of the present invention to provide a method for diagnosing cancer and a method for determining cancer susceptibility.

Please replace the first full paragraph on page three with the following rewritten paragraph:

The inventors of the present invention have studied intensively to accomplish the above-mentioned object and, as a result, have found that the above-mentioned object can be achieved by measuring the activity of a DNA-dependent protein kinase that is an enzyme playing an important role in repair of double-strand DNA ~~break~~ breaks. Thus, the present invention has been completed.

Please replace the first full paragraph on page 7 with the following rewritten paragraph:

Application Serial No.: 10/559,311

Genes (DNA molecules) in vivo receive various damages such as intrastrand ~~cross-link~~ cross-linking, nucleotide modification, nucleotide excision, and duplex intrastrand ~~cross-link~~ cross-linking from the environment. These damages are the main causes of ~~mutation~~ mutations. The accumulation of ~~mutation~~ mutations causes malignant transformation of cells; thus, ~~the mutation is~~ mutations are deeply involved in malignant transformation. Among the above-mentioned damages, double-stranded DNA ~~break is~~ breaks are the most serious DNA damage.

Please replace the last paragraph on page 7 bridging page 8 with the following rewritten paragraph:

The whole picture of proteins involved in a repair mechanism and a repair process of the double-stranded DNA break has being clarified. The outline of the repair mechanism will now be described. Ku-subunit of DNA-dependent protein kinase binds to broken ends of the double-stranded DNA, and recruits catalytic ~~subunit~~ subunits (DNA-PKcs). The activated DNA-dependent protein kinase phosphorylates, for example, XRCC4 protein binding to DNA ligase IV. With this, activated or localized DNA ligase IV rejoins the double strand break of DNA. DNA-dependent protein kinase is an enzyme playing an important role in the repair process of double-stranded DNA ~~break~~ breaks.

Please replace the first full paragraph on page 8 with the following rewritten paragraph:

Application Serial No.: 10/559,311

It has been found that cancer diagnosis is possible by measuring the activity of [[such]] DNA-dependent protein kinase.

Please replace the third full paragraph on page 9 with the following rewritten paragraph:

Lymphoid cells can be obtained from blood by specific gravity centrifugation. Specifically, lymphoid cells can be obtained by layering the blood on Lymphoprep Lymphoprep<sup>™</sup> (manufactured by Nycomed) and centrifuging it to isolate a lymphoid cell fraction.

Please replace the last paragraph on page 10 bridging page 11 with the following rewritten paragraph:

After the completion of the phosphorylation reaction, the reaction solution is spotted on filter paper. After [[the]] washing [[of]] the filter paper, the filter paper is dried with ethanol. The remaining radioactivity on the filter paper is measured with a liquid scintillation counter. The radioactivity per unit protein is calculated as the DNA-dependent protein kinase activity.

Please replace the first full paragraph on page 11 with the following rewritten paragraph:

DNA-dependent protein kinase activity in cells derived from a healthy subject is measured by the same manner as [[the]] described above.

Application Serial No.: 10/559,311

Please replace the first full paragraph on page 17 with the following rewritten paragraph:

Then, a cancer susceptibility determination kit for determining cancer susceptibility by the method for determining cancer susceptibility according to the present invention will be described. The cancer susceptibility determination kit according to the present invention is for determining cancer susceptibility by the above-mentioned method for determining cancer susceptibility and includes at least a peptide substrate phosphorylated by DNA-dependent protein kinase. Examples of the peptide substrate phosphorylated by DNA-dependent protein kinase include the peptide substrates that are described in the above-mentioned cancer diagnosis kit.

Please replace the last paragraph on page 19 bridging page 20 with the following rewritten paragraph:

Lymphoid cells were obtained from blood of the normal group and the cancer patients. Each 20 mL of blood ~~[[of]]~~ from the healthy subjects and the cancer patients was layered on ~~Lymphoprep~~ Lymphoprep™ (manufactured by Nycomed) and was centrifuged at 1500 rpm at 4°C for 30 min. Then, a portion including lymphoid cells was collected to obtain the lymphoid cells. The lymphoid cells thus obtained were frozen and then thawed. This process was repeated three times to disrupt the lymphoid cells. Then, the amount of protein of the disrupted lymphoid cells was measured.

Application Serial No.: 10/559,311

Please replace the first full paragraph on page 20 with the following rewritten paragraph:

A reaction buffer (pH 7.2, HEPES-NaOH containing 100 pmole  $^{32}\text{P}$ -ATP and 990 pmole ATP) containing a peptide substrate (shown as SEQ ID NO:1) that is phosphorylated by DNA-dependent protein kinase was added to the disrupted lymphoid cells at a ratio of 5  $\mu\text{g}$  of the peptide substrate per 1.25  $\mu\text{g}$  of the protein obtained from the lymphoid cells in the above. Then, 0.4 ng DNA was added to the reaction solution mixture to phosphorylate the peptide substrate. As a control, the peptide substrate was added to the ~~disrupted~~ disrupted lymphoid cells without the addition of the DNA.

Please replace the first full paragraph on page 21 with the following rewritten paragraph:

The phosphorylation reaction was conducted at 37°C for 10 min. After the termination of the phosphorylation reaction, the reaction solution was spotted on filter paper. After ~~[[the]]~~ washing ~~[[of]]~~ the filter paper, the filter paper was dried with ethanol. The radioactivity on the filter paper was measured with a liquid scintillation counter. The control value was subtracted from the actually measured value to obtain the observed value.

Please replace the last paragraph on page 21 bridging page 22 with the following rewritten paragraph:

~~Each~~ Two mL of blood was collected from each of 10 healthy subjects (the normal group) and 10 cancer patients who were used in the above. The collected

Application Serial No.: 10/559,311

blood was added to 10 mL of culture solution (RPMI-1640, manufactured by Sigma) containing 2 mL fetal bovine serum, ~~[[and]]~~ 100 µL phytohemagglutinin (PHA, manufactured by Murex) and 40 µL Colcemid (manufactured by Gibco) ~~were added to the resulting mixture~~. The mixture was cultured under 5% CO<sub>2</sub> at 37°C for 48 hr. After the culture, the cells were fixed with methanol/~~acetate~~ acetic acid and were mounted onto a glass slide. Then, chromosome ~~abnormality~~ abnormalities in the lymphoid cells ~~[[was]]~~ were observed by Giemsa stain. Two hundred cells were counted for every sample and abnormality frequency was indicated by the number of chromosome segments per 100 cells.

Please replace the last paragraph on page 22 bridging page 23 with the following rewritten paragraph:

FIG. 1 shows the relationship between DNA-dependent protein kinase activity and chromosome abnormality. FIG. 1 is a graph showing the relationship between DNA-dependent protein kinase activity and chromosome ~~abnormality~~ abnormalities by plotting DNA-dependent protein kinase activity on the horizontal axis and the value of chromosome ~~abnormality~~ abnormalities on the vertical axis. In FIG. 1, the results of the cancer patients are shown by filled circles and the results of the normal group are shown by open circles. With reference to FIG. 1, it is confirmed that ~~the value of chromosome abnormality decreases~~ abnormalities decrease with an increase in DNA-dependent protein kinase activity and, reversely, that ~~the value of chromosome abnormality increases~~ abnormalities increase with a decrease in DNA-dependent protein kinase activity. Additionally, a tendency is observed that the DNA-

Application Serial No.: 10/559,311

dependent protein kinase activity of the cancer patients is lower than that of the normal group. Namely, it is confirmed that cancer susceptibility increases with a decrease in the activity of DNA-dependent protein kinase that is an enzyme playing an important role in the repair process of double-stranded DNA breaks.

Please replace the first full paragraph on page 24 with the following rewritten paragraph:

~~FIG. 2 shows the result.~~ FIG. 2 is a graph showing the measurement results of DNA-dependent protein kinase activity in lymphoid cells of the cancer patients and the normal group. In FIG. 2, DNA-dependent protein kinase activity is plotted on the vertical axis. As shown in FIG. 2, DNA-dependent protein kinase activity in lymphoid cells derived from the cancer patients was significantly lower than that of the normal group. With this result, it is confirmed that cancer diagnosis is possible by measuring DNA-dependent protein kinase activity in lymphoid cells.

Please replace the last paragraph on page 24 bridging page 25 with the following rewritten paragraph:

As described in detail in the above, the presence of cancerous cells can be investigated by the method for diagnosing cancer according to the present invention, whatever the organ or the cause of the carcinogenesis ~~[[is]]~~. Additionally, a tendency to suffer from cancer can be investigated by the method for determining cancer susceptibility according to the present invention.